

INITIATION OF HUMAN SPERM CAPACITATION IN THE ENDOCERVIX*

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IN the initiation of pregnancy, it has long been established that the human endocervix and its secretions do more than provide a conduit for the passage of spermatozoa. The most important of its contributions to the process of fertilization, however, are just beginning to be understood.

It has been accepted that the caliber of the cervical os and the hormonal composition of the endocervical secretions vary according to the phase of the ovarian cycle, and that these changes facilitate or enable the migration of sperm at midcycle but interfere with this process at other times.^{1, 2}

Cervical stenosis, exo- and endocervicitis, and endocrine dysfunction (hypomucorrhea, hypoestrogenism) are among the abnormalities that interrupt normal cervical function. Another cervical source of interference with spermatoc migration was recently documented in studies performed by Behrman and his colleagues,^{3, 4} who showed that spermatozoa could be rendered immobile if they were introduced into the cervical secretions of an immunologically incompatible woman.

One may inquire: Do the cervix and its secretions have additional functions in the events that lead to conception? Studies of norgestrel,† a highly potent progestational material, yielded data whose interpretation permits an affirmative response.

MATERIALS AND METHODS

Norgestrel⁵ ($[\pm] -13 \beta$ -ethyl-17 α -ethynyl-17-hydroxygon-4 en-3-one) is a totally synthesized gonane nor-derivative of testosterone with no estrogenic activity (Figure 1).

All patients studied had been proved by standard tests to have physiologic ovulatory and cervical function. In cycles preceding treatment,

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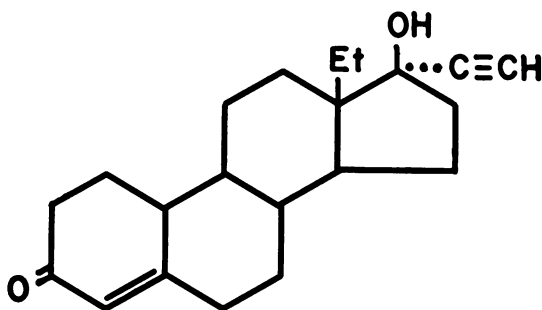
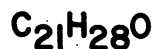


Fig. 1. Structural formula of norgestrel.

postcoital tests (Figure 2) were performed one to five hours after intercourse. Endometrial aspiration (Figure 4) was performed as part of the postcoital test. The fern test (Figure 3) and spinnbarkeit determination were performed at the same time.

The technique of endometrial aspiration was as follows:

1) The endocervix was cleansed with green soap. Swabs were then introduced into the endocervical canal to the level of the internal os in order to remove any remaining spermatozoa.

2) When microscopic study of two successive swabs failed to disclose spermatozoa, 2 cc. of saline solution was injected through a special cannula attached to a 10-cc. Luer Lok syringe introduced into the endometrial cavity. The solution was aspirated and reinjected several times and then centrifuged for 10 minutes; the precipitate was examined under the microscope through a coverslip. At least 30 high-power fields were scanned at each examination.

The other tests were performed by standard methods.⁶

To determine the contraceptive effectiveness of norgestrel, 80 patients received the compound daily in microdoses for 60 days without interruption. Initially three daily dosages were used: 50, 62, and 75 $\mu\text{g.}$, with no exogenous estrogen. Although breakthrough bleeding was less problematic at the 50 and 62 $\mu\text{g.}$ doses, the 75 $\mu\text{g.}$ dosage proved more effective in inhibiting spermatogenic migration, and 65 patients received this dosage.

At midcycle and premenstrually during treatment cycles, postcoital tests with endometrial aspiration and spinnbarkeit and fern testing were

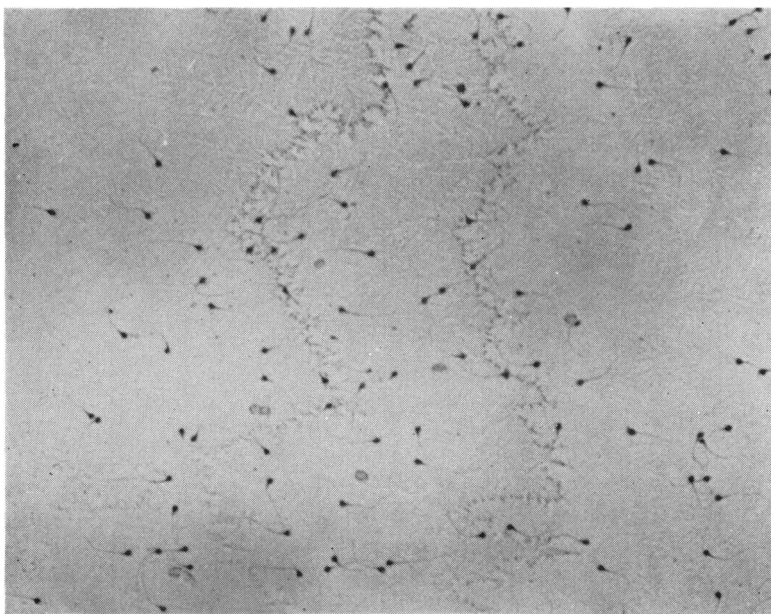


Fig. 2. Pretreatment postcoital test approximately four hours after intercourse.
Note normal spermatozoa in mucus.

performed. Twenty-four hour pregnanediol studies and endometrial biopsies were also done in randomly chosen patients. These studies were repeated in the first posttreatment cycle.

FINDINGS

No conceptions occurred during the period of treatment. Postcoital tests (Figure 5) demonstrated actively motile, normal sperm in even greater concentrations than during the control period. The cervical mucus contained many cellular elements and was viscous. Only two specimens did not disclose fern formation; in the remainder the degree and quality ranged from typical to atypical (Figure 6). Measurements of spinnbarkeit varied from 4 to 10 cm.

In total, 320 endometrial aspirations (Figure 7) were performed in subjects receiving the 75 μ g. dose. Only one poorly motile spermatozoon was seen. Several endometrial biopsies were all considered secretory in type. Pregnanediol determinations gave inconclusive results. Basal body-temperature curves, however, were biphasic in all but two patients. Culdoscopic examination of three patients during the latter part of the second treatment cycle permitted visualization of corpora lutea.



Fig. 3. Pretreatment fern test.

All test results returned to their pretreatment values in the first post-treatment cycle.

COMMENT

The observations indicated that in the relatively small number of patients studied a daily norgestrel dosage of 75 μ g. was adequate for contraception. The evidence suggested, however, that ovulation was not prevented by the compound. The cervical mucus was not rendered hostile or lethal. Spermatozoa in midcycle specimens were actively motile and normal in appearance. The principal effect that could be related to the norgestrel therapy was the virtually complete absence of spermatozoa from the midcycle endometrial aspirates.

Other progestagen-estrogen compounds used for control of fertility have quite different effects, in that the cervical mucus in response to their administration is hostile or even lethal to spermatozoa.⁷

A possible explanation of the contraceptive effectiveness of norgestrel is that the progestagen affected the cervical mucus just enough to interfere with the migration of sperm from the cervical canal. Since no gross changes, either in the spermatozoa or in the endocervical environment, were observed in spite of a systematic search in every case, the

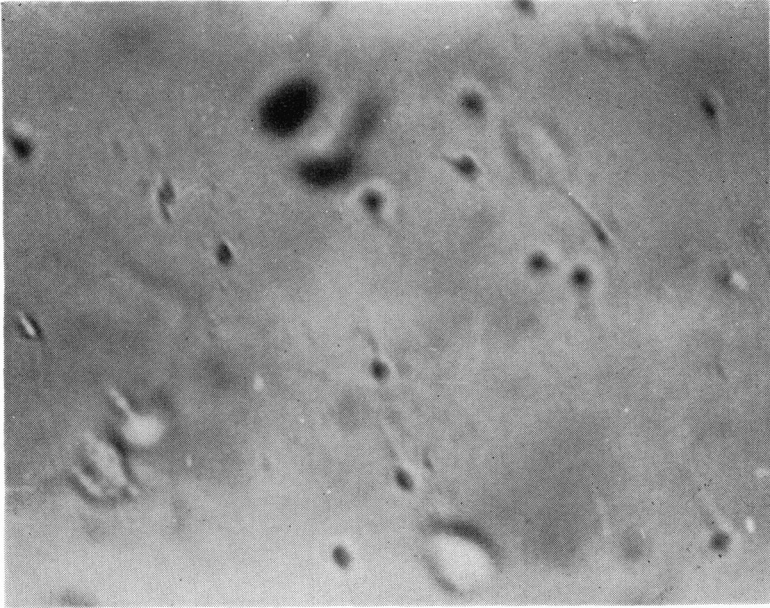


Fig. 4. Pretreatment endometrial aspiration. These spermatozoa were normally motile.

most probable mechanism would appear to involve interference with biochemical changes in the endocervix necessary for spermatic migration.

Evidence from numerous studies in various species of animals strongly supports the opinion that spermatozoa must undergo biochemical changes within the female genital tract if fertilization is to occur.⁸ Austin and Chang (cited in Duncan et al.⁸), who presented the first observations of the phenomenon in lower mammals, termed these reactions capacitation. According to Ericsson,⁸ capacitation is "the physiological and biochemical change . . . which allows for penetration and fertilization of ova."

Investigations in various mammalian species show that the steps in the capacitation process occur at a number of locations in the reproductive tract; the particular sites vary with the species. In human reproduction the phenomenon has never been demonstrated. Investigation of this possibility is handicapped both by necessary restrictions upon physiologic studies in human subjects and also by lack of information concerning the possible loci of the process within the reproductive tract.

The findings in the present study appear to provide indirect evi-

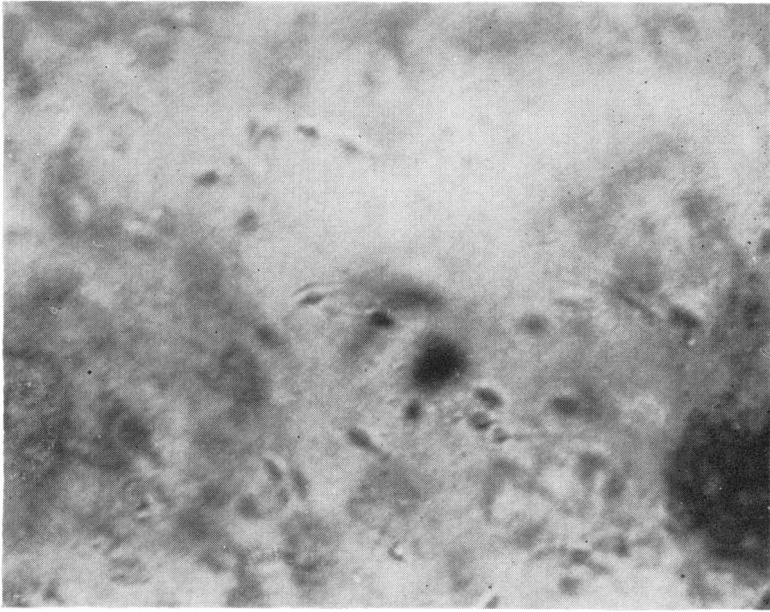


Fig. 5. Postcoital test approximately 3 hours after intercourse in patient given 75 μ g. norgestrel daily.

dence that indicates that capacitation is an essential process in human reproduction, and that its initial step or steps take place in the endocervical canal. The interpretation of the data that best accounts for the contraceptive properties of norgestrel in microdose administration is that the progestagen interfered with biochemical processes essential for further sperm migration. In view of Ericsson's definition, this is tantamount to saying that norgestrel interfered with sperm capacitation in the endocervix.

Since these considerations suggested that similar processes might occur in patients with infertility—especially those in whom diagnostic investigations are uninformative—a number of infertile patients underwent the same tests as those performed in the contraceptive study. Thirty-two patients have been found to date who present normal findings in all parameters except for negative endometrial aspirates after the postcoital test.

A further investigation is being carried out, both to verify the observations on norgestrel and to identify the exact mechanisms by which microdose administration of the progestagen interferes with sperm migration. Other progestagens will be given to patients in

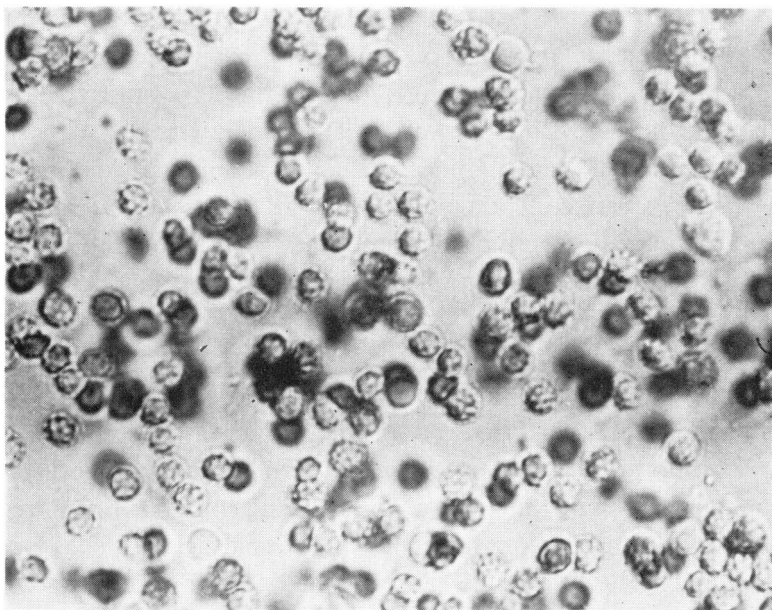


Fig. 6. Endometrial aspirate from same patient as in Figure 3. Note complete absence of spermatozoa.

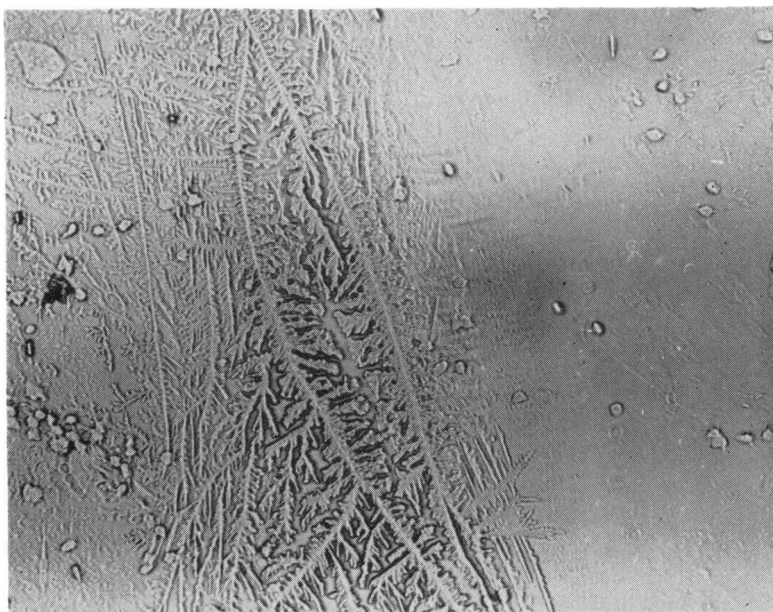


Fig. 7. Fern test performed in patient taking 75 μ g. norgestrel daily.

microdoses, in an effort to determine if the "decapacitating" effects ascribed to norgestrel reflect a capability of any synthetic progestational substance in suitable dosage, or whether a distinctive, as yet unexplained, property of norgestrel is what interferes with sperm migration. The ability of Wy 5090,* an experimental compound, to reverse the decapacitating effects seen both in patients taking norgestrel and in those with infertility associated with failure of sperm migration without other indications of reproductive tract dysfunction is being tested.

A practical corollary of the observations presented here concerns the postcoital test. Up to the present, gynecologists have accepted the view that the test's performance with spinnbarkeit measurement and fern observation was sufficient for evaluation of the endocervical environment and sperm migration. Kleegman and Kaufman recommended the routine performance of endometrial aspiration as part of the postcoital test within two to three hours after intercourse.⁹ The theoretical and experimental basis for this policy was advanced by Moyer,¹⁰ who presented findings that indicate that intrauterine sperm may undergo phagocytosis within several hours after their deposition. In view of these considerations and also of the findings presented here, it appears desirable to perform endometrial aspiration^{6,9} as part of every postcoital test. Without this, normal findings in the postcoital test must be regarded as indeterminate.

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